Review article

Updates on therapy for medullary thyroid cancer in 2021

Mise au point concernant les cancers médullaires de la thyroïde en 2021

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ABSTRACT

Medullary thyroid cancer (MTC) is a rare form of thyroid cancer, frequently linked to a germline or somatic mutation in the RET proto-oncogene. MTC has a good prognosis at the localized stage but prognosis is worse in case of metastases, although there is considerable heterogeneity in progression even in advanced stages. Classical chemotherapy shows little efficacy in this type of cancer. Over the last decade, new effective anti-cancer therapies, in particular multi-targeted tyrosine kinase inhibitors and selective anti-RET tyrosine kinase inhibitors, have changed the management of patients with advanced MTC. The aim of this review is to report the results of studies of these new treatments, and to update the state of knowledge from ongoing studies of treatments such as vectorized internal radiotherapy. In chronic forms, which are incurable but with slow progression, the development of new lines of treatment that can reduce the phenomena of acquired resistance is a major issue.

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RÉSUMÉ

Le cancer médullaire de la thyroïde (CMT) est une forme rare de cancer de la thyroïde. Il est souvent associé à une mutation germinale ou somatique du proto-oncogène RET. Le pronostic est bon aux stades localisés, mais plus sombre en cas de métastase, bien que l'évolution soit très variable même aux stades avancés. Les chimiothérapies classiques sont peu efficaces pour ces types de cancer. Au cours de cette dernière décennie, de nouvelles thérapies efficaces, et notamment les inhibiteurs multi-cibles de tyrosine kinase et les inhibiteurs de tyrosine kinase sélectifs anti-RET, ont modifié la prise en charge des CMT avancés. L'objectif de notre mise au point est de présenter les résultats des études concernant ces nouveaux traitements, ainsi que ceux des études actuellement en cours concernant, par exemple, la radiothérapie interne vectorisée. Pour les formes chroniques, inguérissables mais à évolution lente, le développement de nouvelles thérapies capables de limiter les phénomènes de la résistance acquise est un enjeu majeur.

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1. Introduction

Treatment for metastatic or inoperable medullary thyroid cancer (MTC) has changed greatly over recent years due to the development of new effective targeted anti-cancer therapies. In this review, we will outline the current recommendations for management of localised MTC and then detail the therapeutic arsenal that is now available for treating advanced stage cancers.

2. Recap of epidemiology and prognosis

Medullary thyroid cancers are rare cancers, which represent around 1% of the total number of thyroid cancers. They are well-differentiated neuroendocrine tumors (NETs) arising from a tumoral clone of C cells in the thyroid. Twenty five percent of these cancers are manifestations of a genetic predisposition, multiple endocrine neoplasia type 2 (MEN2), resulting from a germline mutation in the proto-oncogene RET. Fifty to 75% of these cancers found in patients not suffering from NEM2, show a somatic mutation in the RET gene.

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The spontaneous evolution of MTC is slow, similar to the case in other well-differentiated NETs. Prognosis is principally correlated to the stage of the disease: at a localised intra-thyroid stage, the prognosis is excellent, with a 10-year survival of 95.6% while at the stage of regional lymph node invasion 10-year survival is 75.5%. In the metastatic stage, 10-year survival is only 40%, with a median survival of 3.2 years [1].

3. Treatment of localized sporadic forms: American Thyroid Association (ATA) recommendations 2015 [2]

Surgery represents the initial treatment for localized sporadic forms of MTC. Total thyroidectomy must be systematic due to multifocal, small-sized tumors being frequently found, meaning lobectomy is not possible.

MTCs are frequently found to invade lymph nodes, with about 40% showing lymph node invasion at diagnosis, thus central compartment lymph node dissection must be systematically carried out. In the absence of adenopathy seen on ultrasound, the ATA recommendations did not present a consensus position on the necessity of systematic homolateral lateral lymph node dissection and left this decision up to the judgement of the surgical team. Contralateral lateral lymph node dissection is not recommended in this situation. In the presence of adenopathies in the homolateral lateral compartments on ultrasound, contralateral lateral dissection is recommended, depending on the plasma concentration of calcitonin. In fact, according to the original study by Machens and Dralle [3] in 2010, on 300 consecutive patients operated for MTC, contralateral lymph node invasion was never seen in cases where plasma calcitonin concentration was < 200 pg/mL.

These surgical recommendations, different from those that apply to epithelial thyroid cancers, underline the necessity of not ignoring MCT prior to thyroid surgery, and constitute an argument for systematic preoperative assay of plasma calcitonin [4].

The place of cervical radiotherapy in the treatment of MTC is a matter of debate, since the level of proof of its efficacy is weak, and based solely on retrospective studies. A larger study by Martinez et al. in 2010 [5], compared two populations of patients with an MTC and lymph node invasion: 66 patients received adjuvant radiotherapy and 438 patients who did not receive radiotherapy. This study showed no evidence of a beneficial effect of radiotherapy on overall survival. However, given the prognosis for MTC with lymph node invasion is generally favorable, overall survival may not be a useful criterion for evaluating efficacy of treatment. Other studies have used local tumoral control as the evaluation criterion, and several of these studies have argued in favor of the efficacy of radiotherapy [6,7]. These results, with a weak level of proof, need to be balanced against firstly the toxicity of cervical radiotherapy and secondly, the difficulty of surgical reintervention in patients who have previously received radiotherapy.

Thus, the current recommendations are to consider cervical radiotherapy in the case of residual tumor that threatens the upper airway-digestive tract, or in the case of a high risk of recurrence, and where surgical reintervention is impossible.

After initial surgical treatment, the ATA recommends surveillance that is adapted to the results of calcitonin and carcinoembryonic antigen (CEA) assays at 3 months post-surgery. If calcitonin and CEA are undetectable, monitoring would then be solely by clinical signs and biochemistry, using assays for calcitonin and CEA and cervical palpation every 6 to 12 months (for life). If calcitonin and/or CEA are detectable, extension work-up should be based on the levels of circulating calcitonin: in the case of calcitonin < 150 pg/mL residual cervical disease would be the most likely hypothesis [8] and only cervical ultrasound would then be carried out. Conversely, a calcitonin concentration post-surgery of > 150 pg/mL suggests the presence of extra-cervical metastases, and cervical ultrasound should be accompanied by later work-up such as cervicothoracic CT, hepatic MRI, spinal MRI, and bone scintigraphy. The place of FDG PET scanning and FDOPA PET scans in monitoring is debatable since their performance is not optimal and runs the risk of providing falsely reassuring results. At the conclusion of this monitoring, if the residual disease is not identifiable on imaging (that is, is suggested only by biochemical results), the timing of imaging surveillance is dictated by the time to doubling of calcitonin and/or CEA levels, which should be estimated using at least 4 measurements taken at 6 monthly intervals over a 2-year period [2]. A doubling time for calcitonin concentration of less than 1-year is considered as a sign of rapidly progressive disease.

If the disease is identified on imaging, in the case of loco-regional recurrence surgical reintervention and, more rarely, radiotherapy can be considered. In the case of distant metastases, tumor volume needs to be assessed, as does the local risk linked to particular metastatic locations and the intensity of the secretory syndrome (flush, diarrhea). Moreover, the rate of evolution should be assessed in view of the large degree of heterogeneity seen in the profile of disease progression. In fact, as with other well-differentiated neuroendocrine tumors the evolution of MTC at the metastatic stage can be very slow, and some patients can present with spontaneous stable disease over several years. Patients who show little progression, who are asymptomatic and present with low tumor volume can be simply monitored. Those patients with symptomatic metastases, or at risk of becoming so, may benefit from local treatments, for example cementoplasty for a bone lesion. Lastly, patients who present with already a large tumor volume, or who show rapid progression in less than one year, are candidates for normal systemic treatment [9].

4. Systemic treatments up to 2017

Prior to 2012, the only systemic treatments that could be proposed were classic chemotherapy treatments for well-differentiated neuroendocrine tumors: 5-fluorouracil (5-FU), dacarbazine, streptozotocin, or therapies based on doxorubicin. The efficacy of these treatments was mediocre, with maximum objective response rates of 5 to 25% [10,11].

From 2012, first generation tyrosine kinase inhibitors, or multi-kinase inhibitors targeting several cell signaling pathways, became available for use. Cabozantinib and vandetanib, which target signaling pathways of RET and VEGF, obtained regulatory approval to be prescribed in France after prospective trials and phase 3 randomized trials against placebo.

The first trial of this type, published by Wells Jr. et al. in 2012, was the ZETA trial [12], which included 331 patients with inoperable MTC, locally advanced or metastatic, presenting with or without a somatic or germline mutation in RET. These patients were randomized to treatment with Vandetanib or placebo. At inclusion, the patients did not necessarily show disease progression according to RECIST criteria.

The ZETA trial showed a significant lengthening of progression-free survival (PFS) in the patients treated with Vandetanib compared to control, with PFS in the control group being 19 months while the median was not yet measurable for the Vandetanib group at the end of the trial. Additionally, the overall survival (OS) appeared to be prolonged, being > 30 months in the Vandetanib group, though the difference in OS between the two groups could not be demonstrated as survival data were immature at cutoff. The objective response rate (ORR) to Vandetinib was 45% according to RECIST criteria with a prolonged duration of response (DOR) of > 24 months. In the ZETA trial, the impact of RET mutation (either

germline or somatic) on treatment efficacy could not be examined as the RET mutational status was unknown in 40.7% of the patients.

In terms of tolerance, adverse events of grade 3 or 4 were reported in half of the patients. The most frequent of these (> 15% of patients) being diarrhea, hypertension and prolonged QT interval. A third of patients required a reduction in Vandetanib dose, but treatment was stopped in only 12% of patients due to toxicity.

The second trial, published by Elisei et al. in 2013 [13] was the EXAM trial, which included 330 patients with inoperable, locally advanced or metastatic MTC. Patients either presented with somatic or germline RET mutation or did not, and were randomised to treatment with Cabozantinib or placebo. Unlike the ZETA trial, at inclusion patients needed to have shown disease progression according to RECIST criteria over the previous 14 months.

The EXAM trial also showed a prolongation of PFS in patients treated with Cabozantinib compared to placebo: PFS was 11.2 months in treated patients compared to 4 months in those that received placebo. It is important to note that the ZETA and EXAM trial populations were not comparable as the patients included in the EXAM trial showed disease progression at the start of treatment, suggesting disease that was spontaneously more aggressive than in the ZETA trial patients. This may explain the difference in PFS in the patients receiving placebo (4 months for Cabozantinib vs. 19 months for Vandetanib), and so does not permit a comparison of efficacy of the two drugs. In the EXAM trial, OS of treated patients was > 2 years, though it was not possible to show a difference in overall survival between the two groups of patients. ORR, by RECIST criteria, was 27% and the mean DOR was 14 months. RET mutational status was known in 60.2% of these patients and there was no difference observed in efficacy of treatment with Cabozantinib between those patients carrying a RET mutation and those who did not.

In terms of tolerance, adverse events of grade 3 or 4 were reported in three out of four patients, the most frequent of these (≥ 20% of patients) being diarrhea, hypertension and hand-foot syndrome. Four out of five patients required a reduction in dose of Cabozantinib, and 20% interrupted treatment due to poor tolerance.

In 2017, complementary post-hoc analyses were carried out on these two studies. Regarding the ZETA study [14], the subgroup of patients who showed disease progression in the 12 months prior to inclusion were studied in more detail. Within this subgroup there were patients who showed disease progression and were symptomatic at inclusion, and patients who showed progression but were asymptomatic at inclusion. In the first of these groups, prolongation of PFS in patients treated with Vandetanib was significant: 21.4 months in the treated group vs. 8.4 months in the placebo group, $P < 0.0001$. However, in the second group, even though there was a trend, no statistically significant difference was found (median not available for the treated group due to the low number of patients vs. 19.57 months in the placebo group, $P = 0.18$).

Post-hoc analysis of the EXAM trial [15] examined overall survival, and did not show evidence of statistically significant improvement in overall survival in patients treated with Cabozantinib compared to patients who received placebo (26.6 vs. 21.1 months).

In summary, multi-kinase inhibitors of tyrosine kinase thus represent the first revolution in the treatment of MTC due to their efficacy in comparison to the classical chemotherapy treatments that were available up to that time. However, their tolerance was mediocre, leading to frequent reductions in dose, which may compromise their efficacy. Additionally, it was shown that tumors progressively acquired mutations that conferred resistance to these treatments, resulting in therapeutic escape in patients who were initially responders. The most frequent of these is a mutation in valine 804 in the RET gene, inhibiting the binding of the tyrosine kinase inhibitors at one of their binding sites and thus conferring

resistance to treatment. Mutation of the valine at position 804 also results in ligand-independent activation of RET kinase[16].

5. Selective RET inhibitors

From 2017, selective inhibitors targeting the RET pathway became available in phase 1 and 2 trials. The results of these were published in 2020 and 2021 and represent a new revolution in the management of MTC, such that one drug obtained regulatory approval for use even before phase 3 trials were commenced.

The first trial, LIBRETTO-001, [17] studied the efficacy of Selpercatinib and results were published by Wirth et al. in 2020. It consisted of a phase 1-2 trial including 143 patients with either locally advanced or metastatic inoperable MTC. Disease progression according to RECIST criteria was not obligatory but patients had to require systemic therapy. Included patients could also have received prior treatment with another tyrosine kinase inhibitor. The presence of a germline or somatic RET mutation was required for inclusion.

In the phase 2 study, patients received a dose of 160 mg Selpercatinib twice daily. More than two thirds of included patients showed a response to treatment according to RECIST criteria: 69% in the group who had received prior tyrosine kinase inhibitor treatment and 73% in the group that were naïve to tyrosine kinase inhibitor treatment. Another striking result was that 10% of patients showed a complete response to treatment. There was a prolonged duration of response, greater than 1 year in 90% of patients in both pre-treated and naive groups. Eighty-six and ninety percent of patients in each group showed progression-free survival at one year (Table 1).

Improvement in symptoms was not studied in this trial. However, a significant decrease in calcitonin concentration (> 50% decrease compared to initial levels) was observed in 91% of patients, suggesting a likely improvement in symptoms linked to the secretory syndrome, particularly diarrhea.

In terms of tolerance, adverse events associated with treatment have been the habitual effects of tyrosine kinase inhibitors: asthenia, digestive problems, and hypertension. A more specific effect of this treatment is an elevation in transaminases, found in one third of patients. Grade 3 or 4 adverse events associated with treatment were reported in a third of patients, the most frequent amongst these being diarrhea and an elevation in transaminases. One third of patients required a dose reduction in their treatment but only 2% required treatment interruption.

The second trial, ARROW [18], examined the efficacy of Pralsetinib with the results published in 2021 by Subbiah et al. This trial was a phase 1-2 trial including 122 patients in the safety study and 84 in the efficacy study, all with locally advanced or metastatic MTC that was inoperable. Progression during the preceding 14 months, defined by RECIST criteria, was obligatory for inclusion in the trial. Included patients may have already received treatment with another tyrosine kinase inhibitor. The presence of either germline or somatic RET mutation was also obligatory.

In the phase 2 study, patients received 400 mg Pralsetinib once per day. Sixty percent of pre-treated patients and 74% of treatment naïve patients showed an objective response to treatment. The duration of the response was prolonged, since after one year of treatment 92% of treatment naïve patients and 84% of pre-treated patients were still responders. At 12 months, progression-free survival was 75% in the pre-treated group and 81% in the treatment naïve group. In terms of symptoms, 93% of patients who presented with diarrhea linked to calcitonin secretion had resolution of their diarrhea.

In terms of tolerance, adverse events associated with treatment were comparable to those with Selpercatinib. Grade 3 or 4 adverse

Table 1
Efficacy key-points of tyrosine kinase inhibitors in MTC in clinical trials.

Molecule – Trial	Type of trial	Progressive patients at inclusion	Median OS	Median PFS	One-year PFS	ORR	Median DOR	One-year maintenance of response
Cabozantinib – EXAM	Phase III vs. placebo	Yes	26.6 mo	11.2 mo	47.3%	28%	14.6 mo	Not available
Vandetanib – ZETA	Phase III vs. placebo	No	> 30 mo	> 30 mo	> 75%	45%	> 24 mo	Not available
Selpercatinib – LIBRETTO Pre-treated patients Naïve patients	Phase II	No	Not reached	Not reached	82% 92%	69% 73%	Not reached	86% 91%
Pralsetinib – ARROW Pre-treated patients Naïve patients	Phase II	Yes	Not reached	Not reached	75% 81%	60% 74%	Not reached	84% 92%

MTC: medullary thyroid cancer; OS: overall survival; PFS: progression-free survival; ORR: objective response rate; DOR: duration of response.

events that could be linked to treatment were seen in half of the patients, amongst these the most frequently observed were cytopenias and hypertension. A reduction in dose was necessary in half of the patients while only 4% required interruption of treatment due to poor tolerance.

After these spectacular results, Selpercatinib obtained approval from the French regulatory authority in February 2021, as monotherapy, for patients older than 12 years presenting with MTC and carrying a RET mutation, and requiring systemic treatment after treatment failure with first line Cabozantinib and/or Vandetinib. Pralsetinib is, for the time being, only available with a temporary authorization for use (ATU) for patients with metastatic MTC that has progressed after first line treatment with Vandetanib.

6. Future perspectives

There are outstanding questions however concerning these new treatments. In view of the spectacular results obtained in terms of response rate, the question arises as to which first line systemic treatment should be used in MTC, multi-kinase inhibitors or specific RET inhibitors. A phase 3 trial, LIBRETTO-531, is currently underway to try to answer this question. LIBRETTO-531 is a randomised controlled trial comparing first line treatment with Selpercatinib to treatment with either Vandetanib/Cabozantinib, with a crossover at disease progression. Preliminary results for this trial are expected from 2024.

A second question concerns the potential efficacy of this treatment in patients who do not carry a RET mutation, who are not eligible for this treatment, and for whom there is currently no satisfactory second line treatment.

Lastly, a third question concerns the length of progression-free survival with anti-RET treatments. PFS appears to be very prolonged on this treatment, with medians not being reached after 2 years in the LIBRETTO and ARROW trials. However, the development of resistance-conferring mutations has already been observed with these treatments. As a reminder, the V804X mutation in RET does not affect the efficacy of these new treatments since their binding site is different from that of older tyrosine kinase inhibitors. However, tumor biopsies carried out in patients with recurrence of disease evolution and who were initially responders to specific anti-RET treatment, have shown the presence of new mutations conferring treatment resistance [19,20]. This is the case for the G810X mutation, which inhibits the activity of Selpercatinib and Pralsetinib. It is important to emphasise that not all of these new mutations confer resistance to both molecules. Thus, the L730V mutation, which confers resistance to Pralsetinib but not to Selpercatinib, raises the possibility of use of sequential treatments in some patients. More generally, the phenomenon of acquired resistance to treatments targeting signalling pathways in tumors appears to

be the rule, and thus justifies the constant development of new therapeutic molecules to prolong patient survival.

7. Other therapies

The fact that some MTCs show somatostatin receptor expression has been known since the 1990s [21] and is shown by their binding of somatostatin analogs on OctreoScan and PET scans. In this context, the question of efficacy of vectorised internal radiotherapy (VIR) using radiolabeled analogs of somatostatin to treat somatostatin receptor-expressing MTC has been raised. This treatment, which has shown proven efficacy in prospective studies in treatment of neuroendocrine tumors, particularly digestive tract tumors [22], has not thus far been the subject of prospective randomized studies in MTC. MTC can also show expression of the cholecystokinin 2 (CCK2) receptor, which can also be targeted using VIR [23].

A recent review of 19 published studies [24] assembled 117 patients with MTC who received treatment with vectorised internal radiotherapy, in whom treatment efficacy had been evaluated according to RECIST criteria. Only 7.7% of patients showed an objective response to treatment according to RECIST criteria and 55% of patients presented with stable disease. However, the inclusion criteria during the lutatherapy were very heterogeneous and the progressive or non-progressive character of the disease was not always clearly established before treatment. Because of this, it was not possible to confirm that the VIR treatment was responsible for the reported stable disease. The efficacy of this treatment therefore remains to be established in prospective studies.

Regarding immunotherapy, MTCs show only very weak expression of PD1/PDL-1, but expression has been correlated with aggressive forms of the disease [25]. Patients with MTC have thus been included in early trials of immunotherapy. An exhaustive recent review [26] found no efficacy of immunotherapy treatment in MTC to date, though some trials are still ongoing. A recent *in vitro* study has suggested potential efficacy of CAR-T cell treatment, however there are no *in vivo* results thus far available [27].

Lastly, in patients with MTC not carrying either somatic or germline mutations for RET, the most frequently found oncogenic mutations are in RAS isoforms: KRAS, HRAS and NRAS. These mutations have been found in numerous high-prevalence cancers, including colorectal cancer and non-small cell lung cancer, and until very recently were not targetable. In 2021, the first phase II trial reporting on the efficacy of an inhibitor of the G12C KRAS mutation in lung treating cancer was published [28] as were several trials reporting on the efficacy of a HRAS inhibitor in urothelial cancers and certain head and neck cancers [29,30]. Data on the efficacy of these new treatments on MTCs carrying RAS mutations will likely become available in the coming years.

8. Conclusion

Specific inhibitors of RET represent a new therapeutic revolution in the management of metastatic MTC that is progressive and/or inoperable. Their place in the therapeutic strategy for MTC needs to be more precisely defined in the coming years, notably through phase III studies comparing their efficacy to that of multi-targeted tyrosine kinase inhibitors. Lastly, the development of new pharmacological agents will be necessary in the future to combat new mutations that confer tumor resistance, but also for the treatment of MTCs not carrying RET mutations.

Disclosure of interest

The authors declare that they have no competing interest.

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